

Columbia University's Axel Patents: Technology Transfer and Implications for the Bayh-Dole Act

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Context: The Bayh-Dole Act of 1980, which gave federal grantees and contractors the right to patent and license inventions stemming from federally funded research, was intended to encourage commercial dissemination of research that would otherwise languish for want of a patent incentive. The case of Columbia University's Axel patents, which claimed a scientific method to introduce foreign proteins into nucleated cells, illustrates a secondary outcome of the Bayh-Dole Act: the incentive for federal grantees and contractors to pursue royalty revenues from patented research, even for inventions for which commercial use did not require patents.

Methods: This article describes oral interviews with two of the three inventors and a former high-ranking administrator at Columbia; correspondence with several faculty members at Columbia to obtain key royalty figures and information about Columbia's licensing strategy; patent searches; examinations of legal records of court proceedings; and analysis of citation trends for the seminal papers disclosing the invention of cotransformation.

Findings: Columbia University and the inventors profited handsomely from the Axel patents, earning \$790 million in revenues through licensing arrangements that tapped profits from end products made by biotechnology and pharmaceutical companies. Columbia's aggressive effort to extend the patent duration also led to considerable legal expenditures and fierce controversy. In particular, obtaining and enforcing a 2002 patent proved costly, politically difficult, and financially fruitless and attracted intense criticism for behavior unbecoming a nonprofit academic institution.

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Conclusions: This case study raises several important questions about the logic and future revisions of the Bayh-Dole Act: Are revenue generation and financial rewards for inventing valuable technologies legitimate goals for this act? If so, does the federal government need credible mechanisms for oversight of, or checks and balances on, the rights conferred?

Keywords: Biotechnology, history, intellectual property.

THE BAYH-DOLE ACT OF 1980 GAVE FEDERALLY FUNDED grantees and contractors, including universities, a clear and uniform mandate to patent and license inventions stemming from federally funded research. The principal objective of the Bayh-Dole Act was to “use the patent system to promote the utilization of inventions stemming from federally supported research or development . . . to promote the commercialization and public availability of inventions made in the United States by United States industry and labor” (35 USC 200–212).¹ The prospect of patent revenues is not mentioned in the original Policy and Objective preamble to the Bayh-Dole Act, but patent revenues are a foreseeable consequence of owning patents.

The Axel patents claimed cotransformation, a scientific method for introducing foreign DNA into eucaryotic cells. The cotransformation method was discovered by scientists while conducting federally funded research at Columbia University. Five key U.S. patents stemmed from that research, granted in 1983, 1987, 1993, and 2002, and were assigned to (i.e., owned and controlled by) Columbia University. At the same time that the U.S. Patent and Trademark Office (USPTO) was examining the Axel patents, Congress was debating the Bayh-Dole Act of 1980. Although Columbia applied for the first Axel patent a few months before the Bayh-Dole Act took effect, the story of the patenting and licensing of the Axel patents exemplifies features of university technology transfer in the Bayh-Dole era.

In the case of the Axel patents, the primary objectives of Bayh-Dole (utilization, commercialization, and public availability) already were beginning to be realized by the time the patents were granted and would have continued without the patents. The main consequence of patenting and licensing the cotransformation method was that Columbia University established a revenue stream from the commercial products that used the technology, which otherwise would have gone entirely to the companies marketing the commercial products. Without patent rights, then, Columbia University and the inventors would have forgone \$790

million in royalty revenues. The Axel patents also generated litigation and controversy when Columbia tried to extend the duration of patent rights. The patents thus illustrate the revenue potential of patent rights arising from federally funded research, as well as the incentives to extend such rights, leading to litigation and controversy.

Background

On February 25, 1980, three scientists from Columbia University (Michael Wigler, Saul Silverstein, and Richard Axel) filed a patent application claiming a biological discovery that would significantly change biotechnology. *Cotransformation*, as they named their discovery, harnessed mammalian cells' power to produce proteins made from inserted genes.

At the time of the discovery, Axel was an assistant professor in the Institute for Cancer Research and the Department of Pathology, and Silverstein was an assistant professor in Columbia's microbiology department (Silverstein 2005). Michael Wigler transferred into Columbia's PhD program in microbiology after his third year at medical school and was doing a rotation in Silverstein's lab (Silverstein 2005). The initial idea for cotransformation is credited to Wigler, who "had come to the conclusion that we weren't going to make progress in animal cells unless we could manipulate the genetic content of the animal cell" (Wigler 2005). Accordingly, the cotransformation method is sometimes called the *Wigler method*.

Adding DNA to an organism is called *transformation*; similarly, adding two or more genes to an organism simultaneously is called *cotransformation*. Wigler, Silverstein, and Axel devised a way to manipulate the genetic content of a eucaryotic cell (a cell with a defined nucleus) by adding two genes. One, a marker gene, is used to detect whether foreign DNA was successfully taken up and expressed. The marker gene served as a screening tool. The other gene could encode any protein to be studied or produced.

The Wigler method provided a way to introduce genes into eucaryotic cells. A bacterial analog of cotransformation, recombinant DNA, was developed and patented in the early 1970s by Stanley Cohen (Stanford University) and Herbert Boyer (University of California, San Francisco). Cohen and Boyer's invention allowed scientists to "cut and splice" bacterial DNA. It is a powerful biotechnological tool used with great success in molecular biology labs, biotechnology firms, and

pharmaceutical companies and, to this day, is widely used in the research and production of biologics. For researchers attempting to produce functional eucaryotic proteins, however, bacterial recombinant DNA posed problems. Some proteins required cellular “processing,” which bacterial cells cannot perform. But when genes encoding those proteins are inserted into nucleated cells instead of bacteria, they may produce a fully functional protein.

The Wigler method also allowed the production of proteins modified by eucaryotic cells, thereby extending the power of recombinant DNA and significantly increasing the number and type of recombinant pharmaceuticals that could be made using the technology (Fox 1983). Proteins produced by bacterial cells are not usually exported from their place of translation within the cell into the cell’s external growth medium because bacteria are single-celled organisms that retain and use proteins within their own membranes. Eucaryotic cells, by contrast, always have a nucleus and cytoplasm separated by a membrane, creating at least two cellular compartments, and eucaryotic cells often are constituents of more complex organisms that require cell-to-cell communication. Thus, some proteins, such as hormones, receptors, transporters, and channels for water and charged ions, use cellular machinery to facilitate transfer to the cell surface. In addition, for transport to other locations within the organism, some of those proteins (e.g., peptide hormones) are secreted from the cell in which they are produced. Growth factors and hormones, for example, are excreted from cells, and some of those same proteins are candidates to become either drugs themselves (e.g., insulin or erythropoietin) or targets for drugs and are thus relevant to pharmaceutical R&D.

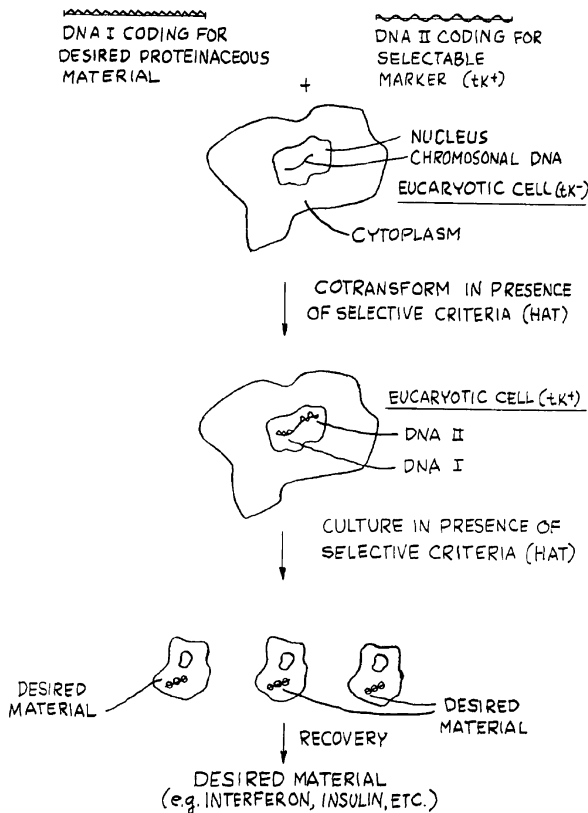
The Wigler Method

Wigler approached Silverstein with the idea of inserting a purified copy of the *tk* gene (which codes for thymidine kinase, a metabolic protein necessary for cell survival) from the Herpes Simplex Virus genome into mammalian cells lacking their own copy of the gene. The cells would then be grown on a medium that inhibits the *de novo* synthesis of thymidine so that the only cells to survive would be those that had taken up the viral *tk* gene. *Cell*, one of the most prestigious journals in molecular biology, published the original paper in May 1977 (Wigler et al. 1977).

By 1979, the Axel group realized they could pair a selective marker (as they had done in 1977 with thymidine kinase) with a gene that could not be directly selected, using a process they called *cotransformation*. They cultured cells with a large amount of the nonselective gene and a small amount of the thymidine kinase gene. Cells that took up the thymidine kinase gene were very likely also to have incorporated the other, much more plentiful nonselectable gene (see figure 1).

U.S. Patent Aug. 16, 1983 4,399,216

COTRANSFORMATION OF EUKARYOTIC CELLS



Source: Image from the original Axel-Wigler-Silverstein patent application (U.S. 4,399,216) filed February 20, 1980, entitled, "Process for Inserting DNA into Eucaryotic Cells and for Producing Proteinaceous Materials."

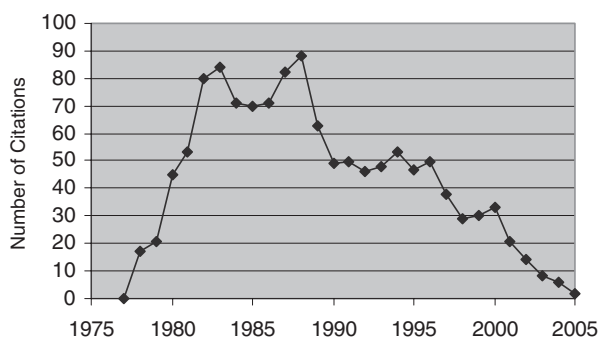
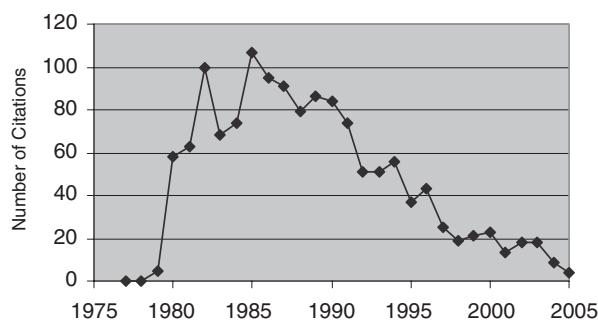
FIGURE 1. Cotransformation Schematic

The cells were then grown on a selective medium, as they were in the 1977 experiments, and probes were used to confirm that the nonselectable gene had in fact been incorporated into the host cell's chromosomes. The 1979 abstract in *Cell* showed the breathtaking power of the new technology: "This cotransformation system should allow the introduction and stable integration of virtually any defined gene into cultured cells" (Wigler et al. 1979, p.77). In other words, cotransformation would allow scientists to make any protein they wanted in nucleated cells.

Earlier attempts to transform eucaryotic cells had been thwarted by low transformation efficiency: few cells took up the foreign DNA (Szybalska and Szybalski 1962). Wigler's method reduced this problem. By using a high concentration of the protein-producing DNA of interest and a low concentration of the marker DNA, if cells took up and produced the marker gene (transformation), they also were likely to have taken up the gene for the other protein of interest (cotransformation). When the DNA was incorporated into the host's chromosomal DNA, it created a stable, self-replicating line of cells producing both the marker protein and the protein of interest. The Wigler method allowed the incorporation of any known gene, procaryotic or eucaryotic, into any mammalian cell that could be grown in tissue culture. The Wigler technology turned mammalian cells into protein-producing machines, a much more efficient way to produce a target protein than the slow, expensive, and laborious synthesis reactions that yielded paltry results.

Citation trends of these two seminal cotransformation papers show how quickly the process was taken up by peers in the scientific community and how widespread the Wigler method became. Figure 2A shows citations of the 1977 paper "Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells," and figure 2B shows the citation trends for the 1979 *Cell* paper "Transformation of Mammalian Cells with Genes from Procaryotes and Eucaryotes."

The Wigler method was immensely useful in both university laboratories and pharmaceutical labs. The process made possible numerous pharmaceutical advances, in turn enabling treatments for diseases from multiple sclerosis to cystic fibrosis. Table 1 provides a sample of drugs developed using the Wigler method, along with the disease they treat.

A. Citations of Wigler et al. 1977 *Cell* PublicationB. Citations of Wigler et al. 1979 *Cell* Publication

Note: These citation graphs show that cotransformation was cited approximately 175 times per year at its peak, compared with a *Cell* Journal Impact Factor (reported by ISI Web of Knowledge) of 39 and 36 in 1998 and 1999, respectively (Journal Citation Reports 2007). *Cell* is, in turn, the most highly cited journal in its field. (Half the papers published are cited never or once; half the papers are cited two or more times: see app. table 5-38, Science and Engineering Indicators 2008 [National Science Board 2008].) The Journal Impact Factor measures the number of times that articles published in a given journal (e.g., *Cell*) over a two-year period were cited by articles in other journals, divided by the total number of articles published in that journal over that same two-year period. Citation trends tend to taper off between fifteen and twenty years after initial publication, when the method either is replaced by a more advanced one or becomes common knowledge. A few caveats must be taken into consideration when interpreting the graph: accuracy of the data, typographical errors or other mistakes in citation, and the intention of the citation, that is, whether the lab is actually using the process or is simply describing the process in a background section.

FIGURE 2. Citations of Wigler et al. 1977 and 1979 *Cell* Publications

The Axel Patents

According to Wigler, the idea to patent the discovery initially came from Richard Axel, and it struck Wigler “as a rather odd thing to do . . . it

TABLE 1
Commercial Drugs Using Cotransformation Technology

Generic Name	Brand Name	Disease/Condition	Manufacturer
Adalimumab	Humira	Rheumatoid Arthritis	Abbott
Agalsidase beta	Fabrazyme	Fabry Disease	Genzyme
Alefacept	Amevive	Psoriasis	Biogen Idec
Alteplase	Activase and Cathflo Activase	Heart Attacks and Stroke	Genentech
Basiliximab ^a	Simulect ^a	Prevents organ rejection ^a	Novartis Pharmaceuticals ^a
Bevacizumab	Avastin	Colon, Rectal Cancer	Genentech
Chorionic Gonadotropin alfa	Ovidrel	Puberty induction, Fertility	Serono
Darbepoetin alfa	Aranesp	Anemia	Amgen
Dornase alfa	Pulmozyme	Cystic Fibrosis	Genentech
Efalizumab	Raptiva	Psoriasis	Genentech
Epoetin alfa	Epogen, Procrit	Anemia	Amgen, J&J
Etanercept	Enbrel	Arthritis	Immunex (now Amgen)
Factor VIII	Advate	Hemophilia A	Baxter
Factor VIII	Recombine	Hemophilia A	Baxter
Factor VIII	ReFacto	Hemophilia A	Wyeth

Factor IX	Benefix	Hemophilia B	Wyeth
Follitropin alfa	Gonal-f	Reproductive Health	Serono
Ibritumomab Tiuxetan	Zevalin	Non-Hodgkins Lymphoma	Biogen Idec
Imiglucerase	Cerezyme	Gaucher Disease	Genzyme
Interferon beta-1a	Avonex	Multiple Sclerosis (MS)	Biogen Idec
Interferon beta-1a	Rebif	Multiple Sclerosis (MS)	Serono
Laronidase	Aldurazyme	Mucopolysaccharidosis 1 (MPS1)	Genzyme
Omalizumab	Xolair	Asthma	Genentech
Rituximab	Rituxan	Non-Hodgkins Lymphoma	Genentech
Somatotropin	Serostim	Growth Hormone	Serono
Tenecteplase	TNKase	Acute Myocardial Infarction	Genentech
Thyrotropin alfa	Thyrogen	Thyroid Cancer	Genzyme
Trastuzumab	Herceptin	Breast Cancer	Genentech

Sources: Drug names and manufacturers from Dudzinski 2004; target diseases from Drugs.com 2007.

^aInformation for Simulect (Basiliximab) from Kestler 2008 and www.pharma.us.novartis.com.

seemed like a long shot, but it wasn't any effort on our part, since the patents were based on manuscripts that we had prepared" (Wigler 2005). Furthermore, aside from the trouble of applying for and being granted a patent, the scientists had no guarantee that the effort would pay off:

We all agreed on the scientific importance of what we had done. Whether this thing would become useful or not—we're all very objective people, and I think we all would have said, "Yeah, there's some probability of being useful, but there's no certainty." It was not clear at the time whether bacteria would be useful for producing all proteins, all medicinal proteins. And it was clearly a possibility that they were not, in which case this would be a better method . . . but there wasn't a guarantee that it would be valuable. (Wigler 2005)

Even after the first patent issued, Silverstein wasn't sure that it would be valuable: "When it was issued, everybody said, 'Gee that's terrific,' and I pointed out to them, 'Yeah, it's terrific if we get somebody to actually license it'" (Silverstein 2005). If the scientists' viewpoint seems somewhat naive, one reason may be that patenting at universities had not yet become commonplace: it was a "nice to have" rather than a "need to have." Concerns about university patenting also had not reached the intensity they would in coming years. The technologically related Cohen-Boyer patent had been granted to Stanford and the University of California only recently, and biotechnology was a nascent field. While university patenting was not unusual in organic chemistry, engineering, and solid-state physics, it was relatively new to molecular biology, and the economic, social, legal, and ethical questions about patenting were just becoming the subject of debate.

The inventors informed Paul A. Marks, then the vice president of health sciences at Columbia University, of their decision to patent. They went to Marks because Columbia did not have a technology transfer office at the time. As Marks recalled in an interview, "I don't think the Columbia University industrial licensing group was very sophisticated, and they were not encouraging or enthusiastic about going forward to try to get a patent on this work" (Marks 2005). Marks then went to the provost, Michael I. Sovern, who referred the inventors to the law firm Cooper-Dunham, where attorney John White (who had received his BS in chemical engineering, MA in chemical biology, and MPh in

biophysical chemistry from Columbia) handled the patent prosecution. Although the scientists were involved in the initial drafting process, the legal expert did most of the writing and framing of claims. Both Wigler and Silverstein confirmed that their role was negligible once the initial draft was completed. Silverstein recalled, "I do remember the hours spent with John White, who was the lead attorney at that time on this series of patents . . . he asked us lots of good questions, and we had to figure out answers" (Silverstein 2005).

The patent application was filed on February 25, 1980. The claims in the application, which included any cell transformed via the method of cotransformation, anticipated by about four months the landmark Supreme Court decision in *Diamond v. Chakrabarty*. *Diamond v. Chakrabarty* was a watershed for biotechnology patenting because in that decision the Supreme Court made clear that living organisms were patentable subject matter.² While some of the claims in the Axel patents pertained to general methods and not organisms per se, the Axel patents also included claims covering cell lines that produced proteins of interest, so the Supreme Court decision made it likely such claims would be upheld in court. This strengthened Columbia's hand in licensing its patents.

That year, the Bayh-Dole Act also was being debated in Congress and was passed in a lame duck session on December 12, 1980 (see Stevens 2004). Its stated purpose was to encourage the dissemination and commercialization of federally funded research. Although the Cohen-Boyer and Axel patents are sometimes cited as exemplars of Bayh-Dole, the first of the Cohen-Boyer patents had been granted ten days before the Bayh-Dole Act passed in Congress, on December 2, and Columbia had applied for the first Axel patent ten months before Bayh-Dole was enacted. Because Bayh-Dole had not yet been implemented, the National Institutes of Health (NIH), which had funded the research, could have asserted ownership of the patents, imposed requirements on them (e.g., required the institution to send annual reports, allowed nonprofit institutions to license them free of charge, etc.), or decided not to apply for patents at all. At that time, if an institution wanted to patent an invention stemming from research funded by the NIH, it had to request the right to do so, often under terms of an Institutional Patent Agreement and sometimes as an ad hoc request.

Columbia sent a letter to the NIH on April 4, 1980, seeking permission to apply for and control patents stemming from the Axel group's

work, six weeks after it filed the patent application (Mowery et al. 2004). Columbia specifically sought permission to patent and then license the technology exclusively (e.g., to license the patent to just one company or institution, thereby denying all other companies or institutions the right to use the patent's protected technology except through the exclusive licensee). On February 24, 1981, the NIH wrote back, giving permission to patent and to assign the patent to Columbia but denying the request to offer an exclusive license unless Columbia could demonstrate that nonexclusive licensing was not viable (Miller 1981). The NIH also required that Columbia give the U.S. Department of Health and Human Services (HHS) copies of any licensing agreements and provide a detailed annual report

regarding the development and commercial use that is being made and is intended to be made of the invention, including the amounts and source of money expended in such development and such other data and information as the HHS may specify. After the first commercial sale of any product embodying the invention, such report shall specify the date of the first commercial sale and shall include information relating to gross sales by licensees, and gross royalties received by the University. (Miller 1981)

The NIH also specified the royalty share for the university and the inventors and stipulated that any potential licenses "include adequate safeguards against unreasonable royalties and repressive practices," a point to which we will return later (Miller 1981).

While Columbia did request the right to exclusively license the Axel patents, this was by no means the only option, or even the one that Columbia preferred. Paul Marks said that Columbia's attitude was that it would not hurt to ask. In retrospect, Marks commented, "I think it's very fortunate for a number of reasons that we didn't succeed because I don't think we fully anticipated the sort of impact that this discovery would have on drug development" (Marks 2005).

In 1982, Columbia formed the Office of Science and Technology Development (OSTD), which took over the administration of the patent application (Mowery et al. 2004). The office has since gone through two name changes and is now called the Science and Technology Ventures Office. The first of five patents was granted on August 16, 1983 (U.S. Patent 4,399,216, hereafter '216).

Five days before the first patent was granted, Columbia's OSTD filed a divisional application covering the cotransformation process using a phage or plasmid vehicle. A divisional application shares the priority date (initial filing date) from a previously filed patent application in which more than one invention was disclosed and also claims a separate invention that was a part of the original patent application. Divisional applications are generally a response to the patent office's objection that the application claims more than one invention. The applicant then chooses to pursue a subset of claims as one invention from the original application and can opt to file a divisional application containing claims for another invention.³ Divisional applications are distinct from continuation applications. Continuation applications also retain the priority date from an earlier application, but they are filed when the applicant wants to revise the claims.⁴ The application filed on December 7, 1980, was the first of nine divisional or continuation applications that Columbia was to file stemming from the original February 1980 application.

The divisional application became the second Axel patent on January 6, 1987 (patent 4,634,665, hereafter the '665 patent). Because this patent was very similar in claims to the original '216 patent, Columbia agreed that the '665 patent would expire on the same date. This kind of agreement is known as a *terminal disclaimer*. When an inventor obtains more than one patent on a closely related invention, the inventor agrees to "disclaim" the extra duration that would normally come with the later-issued patent, so that the rights end with expiration of the original patent on the related inventions from the original patent application. On the basis of the '665 patent, Columbia filed divisional and continuation patent applications in 1986, 1989, and 1991. The applications in 1986 and 1989 were abandoned, but the 1991 application turned into Columbia's third Axel patent on January 12, 1993 (patent 5,179,017, or the '017 patent). The '017 patent also was subject to a terminal disclaimer, expiring with the first and second patents. In this way, the '216, '665, and '017 patents were considered by both Columbia and the patent office to be in the same invention family. Together, the three patents cover the Wigler method in any eucaryotic cell, specific markers, any proteins produced with the process, and cell lines producing the desired proteins, called *transformants* (Dudzinski 2004). On the basis of the 1993 application, Columbia filed more divisional and continuation

applications in 1992 (one application), 1994 (one application), and 1995 (three applications, one on February 27 and two on June 7).

The timing of the two June 7, 1995, applications was significant: the next day, amendments to U.S. patent law took effect, bringing the law into harmony with most other jurisdictions around the world. For applications filed on or after June 8, 1995, Congress changed the length of a patent term from seventeen years from the date of the patent issue (and publication) to twenty years from the date that the application was filed. This moved the starting point of the patent term from the finish line of the patent examination (obtaining a patent) to the starting line (date of filing a patent application), which in turn changed the underlying incentives in the patent examination process.

This change made the practice of filing numerous continuation and divisional applications to keep the application open less attractive as a strategy to extend patent rights, since the patent term would no longer be extended by protracted examination proceedings. After June 1995, the patent examination proceedings instead ate into the valuable patent duration. But because Columbia's last two continuation applications were filed a day before that change took effect, any resulting patents still would last for seventeen years from the date they were granted.

On September 22, 1992, Columbia was granted U.S. 5,149,636 (the '636 patent). This patent resulted from a different set of original applications (in other words, it was not a divisional or a continuation of the original 1980 application). It was the third continuation application stemming from an original application filed March 15, 1982. The '636 patent claimed a method for cotransforming eucaryotic cells with multiple copies of foreign DNA fragments. This patent will expire in September 2009, as it was a separate invention not subject to the terminal disclaimer that Columbia agreed to for the previous three patents. The inventors named on the '636 patent are Richard Axel and James M. Roberts (who was a graduate student in Axel's lab at the time), and it was licensed as part of a package with the other three Axel patents (Kestler 2008).⁵

In August 2000, the three original Axel patents expired, thereby ending the obligation for companies with licensing agreements to pay royalties. On September 24, 2002, however, the U.S. Patent and Trademark Office granted a fourth patent stemming from the original application (patent number 6,455,275, expiration date September 24, 2019). The

continuation application resulting in this patent was filed just before the June 1995 deadline. If Columbia University had waited until June 8, 1995, under the new rules, the '275 patent would have expired in February 2000, twenty years after the original filing date (i.e., it would have expired before it was granted in 2002). But under the old rules, the patent term for the 2002 patent extended for seventeen years from its date of issue in 2002. Figure 3 shows a chronology of the U.S. patents.⁶ Another June 7, 1995, continuation application is still pending.

Commercialization and Licensing

By the time the first Axel patent issued in 1983, many research laboratories were already using cotransformation: the citation graphs in Figure 2 show that the '77 and '79 papers were cited more than eighty and more than sixty times that year, respectively, and a September 2, 1983, *Science* article noted that "the procedures developed by Axel and his colleagues are being used extensively in basic research" (Fox 1983, p. 933). As Harvard University molecular biologist James Barbosa put it, "The patent's process has been in use all over the academic world since '77 . . . it's been such a boon in getting mammalian cell gene transfer off the ground that it has almost become a laboratory reagent" (Mowery et al. 2004, p. 157).

To some in the scientific community, a patent on a widely used research process was frightening and offensive because of its potential to deter laboratory work owing to high costs and strict protection of patented materials. Some of these fears were unrealistic and were based on misunderstanding patents or failing to see how patent owners could manage their patents to avoid impeding research. Columbia never required fellow researchers at nonprofit institutions to license the patent, for example, and it did not collect licensing fees from nonprofit research (unlike the Wisconsin Alumni Research Foundation, which initially charged research institutions a licensing fee on stem cell patents; see Cohn 2007; Editorial 2007; Rabin 2005). The scientific community was nonetheless concerned. Barbosa went on to say that "the fact that the process has been patented just doesn't seem right" (Mowery et al. 2004, p. 157).

Patents and Licensing Events	Technical and Legal Events
	1977 – Wigler et al publish results of transformation experiments with herpes simplex virus genetic material
	1979 – Wigler et al publish <i>cotransformation</i> method in <i>Cell</i>
1980 – Application 124,513 filed	1980 – <i>Diamond v. Chakrabarty</i> decided in U.S. Supreme Court; Bayh-Dole Act takes effect
	1981 – Letter from NIH to Columbia denying request for right to exclusively license Axel patents
1983 – Patent 4,399,216 issued; divisional application 552,408 filed	
1986 – (Divisional) 915,273 filed	
1987 – Patent 4,634,665 issued	
1989 – (Continuation) 346,089 filed	
1991 – (Divisional) 716,915 filed	
1992 – (Continuation) 866,800 filed	
1993 – Patent 5,179,017 issued	1993 – Columbia University files infringement lawsuit against Roche Diagnostics
1994 – (Continuation) 217,007 filed	1995 – Amendment to U.S. patent law takes effect; patent term counted from date of filing rather than date of issue
1995 – (Continuations) 395,520; 484,136; and 477,159 filed	
2000 – Patents '216, '665, and '017 expire under terminal disclaimer	2000 – Senator Judd Gregg (R-NH) tries to extend Columbia's patent rights through Hatch-Waxman Act
2002 – Patent 6,455,275 issued	2002 – Roche Diagnostics pays damages to Columbia University
	2003 – Biogen et al bring suit to Columbia University
2004 – Columbia University signs Covenant Not to Sue, nullifying '275 patent by giving up the right to collect royalty revenue from that patent*	

* Columbia University is still pursuing continuation 477,159.

FIGURE 3. Time Line of Key Developments in Patenting and Licensing of Axel Patents

From the perspective of Columbia's licensing office, the fact that the process was in wide use posed a potential problem: That is, if academic laboratories were already using the process, pharmaceutical and biotech firm R&D laboratories were using it, too. Furthermore, because the patents primarily covered a process rather than a final product, infringement would be difficult to prove. A final product would not necessarily "embody" the invention or reveal how it was made. In the

beginning, Columbia's licensing strategy was to identify firms that were using the technology and advise them to take out a license. To do this, "Columbia licensing personnel examined the patents, end products, and scientific publications of industrial firms . . . and informed these firms that if they were using the cotransformation process to produce proteins, they must pay royalties to Columbia" (Mowery et al. 2004, p. 157).

Columbia's OSTD made it clear that if infringing companies did not comply, they would face legal action. The fact that this step was necessary is an indication that industry had adopted the method without a patent incentive. Columbia also recognized, as Stanford University did with the Cohen-Boyer patents, that if it charged too much for licenses, it would invite challenges to the patents, requiring unwelcome and expensive litigation to enforce patent rights. Instead, Columbia charged an annual fee of \$30,000 and relatively modest royalty streams of a small percentage of final product revenues in the hopes that companies would choose to take out a license rather than challenge the patents in court (Sampat 2000).

To encourage companies to sign up early, Columbia took another lesson from Stanford's handling of the Cohen-Boyer patents, by offering reduced licensing fees to firms that took out a license before June 1, 1984 (Sampat 2000). The "early bird" terms were \$20,000 annually, with royalty rates of 1.5 percent of sales for finished products, 3 percent of sales for bulk products, 12 percent of sales for basic genetic research products, and 15 percent of cost savings from process improvements. The standard terms after the "early bird" incentive were \$30,000 annually and royalties of 3 percent, 6 percent, 15 percent, and 18 percent for the categories just listed (Sampat 2000). According to Jeffrey Kestler, associate general counsel of the Patent and Licensing Group at Columbia University, the original standard licensing terms for the Axel patents also included a provision allowing the licensee "to take advantage of more favorable rates that might be granted to other licensees in certain circumstances, which prevented concerns that a licensee would be prejudiced by early adoption of the technology," and a royalty stacking provision lessening the amount owed to Columbia if the licensee paid royalties to other patent owners on the same product (Kestler 2008). Also according to Kestler, "the intent of the licensing program was to license the patents as widely as possible and to provide licensees with as much flexibility as possible" (Kestler 2008).

Ten firms signed up under the “early bird” agreement, and Columbia continued until at least the 1990s to identify potential users and advise more companies to take out a license. As coinventor Saul Silverstein put it in an interview, “They [Columbia] were fairly aggressive at pursuing some of the companies who we knew were making pharmacologically active drugs that would require using this technology” (Silverstein 2005). All in all, thirty-four firms licensed the cotransformation technology, ten as early birds and twenty-four under the regular license agreement (Sampat 2000).

Columbia’s threats of litigation were not idle. In 2000, Columbia brought action against Roche Diagnostics (formerly Boehringer Mannheim) for patent infringement, in a complicated case also involving the therapeutic protein erythropoietin (EPO). Columbia alleged that EPO made in cotransformant cells at the Genetics Institute (which was acquired by Roche) was shipped to Roche in 1985, infringing the Axel patents.⁷ Judge Nancy Gertner ultimately awarded Columbia \$1.2 million in damages from Roche.

Revenue

Over their seventeen-year term, the Axel patents earned \$790 million in royalties, which was divided between the university and the inventors as outlined next.⁸ Year-by-year data were not available from Columbia’s office of Science and Technology Ventures but are based on the similar history of the Cohen-Boyer patents (see Feldman, Colaianni, and Liu 2007). Most of the royalty revenues were earned in the last few years of the patent’s life, when derivative products were generating royalty-relevant revenue for the licensees.

Because the Axel patent application was filed before the Bayh-Dole Act took effect, Columbia was obligated to follow the royalty-sharing scheme specified by the government in the letter denying its request to offer an exclusive license (Miller 1981). The inventors would share 50 percent of the first \$3,000; 25 percent of the income between \$3,000 and \$13,000; and 15 percent of the income exceeding \$13,000. After deducting expenses of obtaining and defending the patents, the remaining royalty income would “be utilized for the support of educational and research pursuits” (Miller 1981). Following this formula, the three inventors (and a fourth, unnamed, person) would have divided more

than \$110 million (Silverstein 2005).⁹ After Columbia University deducted 20 percent of the remainder for the expenses of obtaining and defending the patent, more than \$530 million would remain for use in the inventors' laboratories and general university funds.

The revenues from the Axel patents contributed a significant fraction of Columbia's patent revenues, shown in table 2, which compares royalty revenues with R&D expenditures. Not all royalty income goes to R&D, but this figure indicates the revenues from technology licensing compared with R&D expenditures, a rough proxy for how much an institution relies on licensing revenues compared with other R&D funding streams.¹⁰ Columbia ranked second and third among U.S. institutions on this indicator in FY 1999 and 2000. Columbia's royalty revenues were equivalent to 32 percent (1999) and 44 percent (2000) of R&D expenditures in those final two years of the Axel patents' term.¹¹

Beyond the general terms in the government letter, we do not have detailed data about how the Axel patents' royalty revenues were divided among the inventors' laboratories and the university. We do know, however, how Columbia used some of the funds. According to Jeffrey Kestler, the university's share was used to support the Columbia University Medical Center, as well as a fund for general university purposes, such as establishing a new Department of Biomedical Engineering at the Fu School of Engineering; the interdisciplinary Judith P. Suzlberger, MD, Genome Center; and the Columbia University Earth Institute (Kestler 2008).

Expiration and Controversy

When the first three Axel patents ('216, '665, and '017) were set to expire on August 16, 2000, Columbia's administrators spoke of the impact: "In the near future, our revenues are likely to drop sharply," warned Jonathan Cole, then Columbia's provost, in an October 2000 internal document" (Wysocki 2004, p. A1).

Columbia took measures to extend the patents' term. In March 2000, Columbia turned to Senator Judd Gregg (R-NY), a Columbia alumnus, who began a nearly five-month effort to pass legislation that would enable Columbia to get a fifteen-month term extension on the three patents

TABLE 2
Percentage of Total R&D Funding Accounted for by Licensing Revenue for
Top Ten U.S. Universities

FY 1999		
University	Licensing Revenue (1999 US\$)	Licensing Revenue as Percentage of R&D Budget (%)
Florida State University	57,313,014	43.20
Columbia University	89,159,556	31.93
Yale University	40,695,606	12.88
Michigan State University	23,711,867	10.88
Tulane University	7,572,483	8.67
Michigan Technological University	2,222,872	7.92
University of Florida	21,649,577	7.72
Emory University	15,257,565	7.42
New York University	10,700,000	7.18
Stanford University	27,699,355	6.64
FY 2000		
University	Licensing Revenue (2000 US\$)	Licensing Revenue as Percentage of R&D Budget (%)
Dartmouth College	68,427,222	74.62
Florida State University	67,497,034	49.53
Columbia University	138,562,416	44.54
Brigham Young University	5,072,274	29.73
Georgetown University	26,000,000	21.14
University of California System	261,522,000	12.55
Michigan State University	25,721,007	11.29
University of Florida	26,267,649	8.91
Stanford University	34,603,000	7.79
Tulane University	6,826,436	7.60

Sources: Data compiled from FY 1999 and FY 2000 licensing revenue data from the Association of University Technology Managers licensing survey (courtesy of Bhaven Sampat, Columbia University).

set to expire in August 2000 (Rosenberg 2000). Gregg attempted to amend the Hatch-Waxman Act of 1984 (also called the Drug Price Competition and Patent Term Restoration Act) to allow Columbia to apply for a patent extension. One of the Hatch-Waxman Act's provisions allows pharmaceutical companies to apply for patent-term extensions to

compensate for the time out of the patent term consumed by FDA approval procedures. Gregg argued that because the cotransformation process was used to make pharmaceuticals, which were subject to FDA approval, Columbia should be able to extend the patent terms.¹²

If Gregg's bill had become law and had been applied to the Axel patents, Columbia would have been able to extend its patents for fifteen months, earning the university another \$70 million to \$100 million (Wysocki 2004). In May 2000, Senator Gregg tried unsuccessfully to insert a 350-word amendment¹³ into an agricultural spending bill to allow nonprofit institutions whose inventions led to five or more new drugs to apply for patent-term extensions (Rosenberg 2000). He again tried in June via a military spending bill, but after both these attempts failed, he gave up (Rosenberg 2000). In retrospect, legal scholars and others reflected that if the extension had become law, it would have established a precedent: Pharmaceutical and other companies might have become emboldened to try to extend patents on other methods or processes, leading to higher development costs and more complicated licensing arrangements (Fram 2000).

When this legislative effort became public, it caused a significant backlash. Gregg and Columbia received "a storm of criticism from drug manufacturers, consumer groups, and Members of Congress, including Senator Edward M. Kennedy" (Rosenberg 2000, p. A1). Senator Gregg characterized the fight as Columbia, a "poor little university," up against "a fair amount of greed on the part of the drug companies" (Kane 2000, p. 16). Representative Henry A. Waxman, coauthor of the Hatch-Waxman Act, felt that Gregg's proposal "ha[d] nothing to do with the original intent of the act. . . . On the contrary, it [ran] counter to what we accomplished" (Rosenberg 2000, p. A1). Senator Hatch, the other main sponsor of the Hatch-Waxman Act, expressed misgivings, and New York's Senator Patrick Moynihan supported Gregg; but Senators Harkin and Durbin vowed to block the amendment on the floor of the Senate.

Despite the opposition and press controversy, Columbia officials stood by their decision to try to extend the life of the patent. Michael Crow, then Columbia's executive vice provost (and a professor of science and technology policy in Columbia's School of International and Public Affairs), defended the university's measures by pointing out that much of the money went back into research: "The three inventors split 20 percent of the royalties, he said, so each reaps

millions annually. The rest—minus some administrative costs—goes to research. ‘It’s not like we’re taking the money and buying hotels’” (Fram 2000).

After the extension measure failed, a Columbia spokesperson said that there was not a “next step in this patent extension story . . . there’s just no way to go back after it expires” (Dudzinski 2004, p. 597).

The university, however, was still pursuing the divisional applications it had filed on June 7, 1995. As described earlier, on September 24, 2002, two years after the original Axel patents expired, U.S. Patent 6,455,275 was issued, claiming specific Chinese hamster ovary (CHO) cells into which a DNA construct was inserted. After the patent issued, Columbia sent letters to its former licensees alerting them that they would once again owe royalties for another seventeen years.

The licensees pushed back: in 2003, Genentech, Immunex, Amgen, Biogen, Genzyme, Abbot, Wyeth, Genetics Institute LLC, Johnson and Johnson, Serono, Baxter, and Ares all filed suit against Columbia, asking the judge to find the ’275 patent invalid and unenforceable, arguing that the ’275 patent was not distinct from the earlier Axel patents (Dudzinski 2004).¹⁴ Thomas Bucknum, then the executive vice president of Biogen, remarked, “It’s the same invention, and that’s why we decided we just wouldn’t pay” (Wysocki 2004, p. A1).

In court, Columbia was represented by eight lawyers, prompting Judge Mark L. Wolf to comment, “I thought Columbia was a nonprofit organization who couldn’t afford this litigation” (Wysocki 2004, p. A1). Judge Wolf’s conclusion was that

the timing of its [the ’275 patent] issuance strongly suggests that Columbia deliberately delayed obtaining a patent that it always intended to secure in order to make it effective just as the other Axel patents expired and thus increase its commercial value by maximizing the period in which the public would have to pay Columbia royalties for the use of the Axel patents.¹⁵

The press got hold of the story and began to compare Columbia with “an aggressive U.S. corporation” (Wysocki 2004, p. A1), accusing the university of “submarine patenting” (Marshall 2003, p. 448).

Dan Ravicher, a patent attorney and founder of the Public Patent Foundation (PubPat, a nonprofit organization that seeks to “protect the public from the harms caused by wrongly issued patents and unsound

patent policy”) also took aim at Columbia’s new patent (Ravicher 2004). In February 2004, PubPat filed a request for reexamination *ex parte* of the ’275 patent, asserting that “none of Axel et al.’s four patents are patentably distinct from one another” and that the ’275 patent had been issued only after numerous rejections for double patenting and seven years of “unreasonable and unexplainable delay on the part of Axel et al. and changes in the personnel examining the application” (Ravicher 2004). Ravicher charged that the ’275 patent was invalidated by the three prior Axel patents’ claims.¹⁶

Faced with these lawsuits, the judge’s opinion, and reexamination requests, Columbia signed a covenant not to sue, effectively relinquishing its right to enforce claims in the ’275 patent against the plaintiffs. On October 12, 2004, Columbia further agreed to refrain from suing not only the plaintiffs but also any future litigants. But Columbia did maintain that the ’275 patent was valid: “In granting this covenant to plaintiffs, Columbia in no way concedes plaintiffs’ allegations that the ’275 patent is invalid, unenforceable, or not infringed. To the contrary, Columbia categorically rejects all such claims by plaintiffs” (Attorneys for the Trustees of Columbia University in the City of New York 2004). This assertion was undermined on March 15, 2007, when the patent examiner responsible for the case at the U.S. Patent and Trademark Office rejected the patent’s claims.¹⁷ Columbia submitted a brief in June 2008 appealing this decision to the Board of Patent Appeals and Interferences (BPAI), and it might appeal to the courts if the BPAI concurs with the examiner.¹⁸

Columbia’s final continuation application (application 477,159) of the original Axel patent application, filed on June 7, 1995, is still being prosecuted and may therefore result in the issuance of a patent. Dan Ravicher, founder of PubPat, wrote, “To my knowledge, they are still pursuing [the second application] vigorously, as they are a reissue of the ’275 patent” (2005). If the patent is reissued, many of the plaintiffs from the earlier double patenting case have indicated that they will challenge its validity.¹⁹

One final point about government oversight is relevant to the actions that Columbia took after the original Axel patents expired in 2000. Recall that the government letter stipulating terms to Columbia called for licensing “safeguards against unreasonable royalties and repressive practices” (Miller 1981). Presumably, the NIH still had rights stemming from that letter, but our Freedom of Information Act (FOIA) request to

the NIH caused confusion about whether the inventions were covered by Bayh-Dole, and it cast doubt on whether anyone in government was monitoring the case or was even aware that the government had rights to exercise. The Miller letter apparently came to light after the patent litigation already had begun. If the government letter had been more publicly available, lawyers concerned about the 2002 patent might have been able to avoid litigation to challenge the patents and instead could have petitioned NIH to act administratively, at a considerably lower cost and perhaps with the same outcome. While the government stipulated conditions on licensing the patents, it apparently did not take action when Columbia engaged in highly public and controversial actions to extend its patent rights, first through Congress and then by obtaining the patent in 2002. The NIH apparently never invoked this clause, suggesting that it had limited ability to monitor compliance with the “safeguards” it required of Columbia in its licensing via the letter agreement. It may even have been unaware of the government’s rights even in this case, in which both Columbia and the federal government explicitly agreed to such rights.

Conclusions and Policy Implications

The Axel patents also have implications for the Bayh-Dole Act. That is, this case highlights the need to decide explicitly, as a matter of policy, whether generating revenues for research and education is a valid goal of the technology transfer framework, in addition to the original rationale of inducing commercial use that would not occur without patent incentives. The Axel patents were not crucial to facilitating the transfer of technology, in the sense of being necessary for commercial use. Skilled researchers at both universities and biotechnology companies could replicate cotransformation based on scientific papers alone (Fox 1983; Mowery et al. 2004). Instead, the main effect of the patents was that Columbia earned royalty revenues when the commercial use of the Wigler method became successful. If Columbia had not patented cotransformation, the revenues would have gone to private industry, with little or no return to Columbia.

Many scholarly articles characterize such royalties as a “tax” on innovation. The royalties do indeed act like a tax in one respect: they tap revenue. They differ from a “tax,” however, in that they are specific to a

licensed invention; they do not involve the direct hand of government in collecting the revenue; and they confine expenditure of the revenue only to uses (research and education) that are generally considered public goods. The revenues go to the inventors and institutions responsible for producing valuable inventions, thus rewarding them for their discoveries and resonating with John Locke's ideas about incentives from property ownership that are deeply rooted in law (Mosoff 2001). Consequently, it is somewhat inaccurate to call this a "tax on innovation," but the wisdom of such revenue diversion is certainly a legitimate policy question.

The Axel patents raise the question whether the revenue-generating potential of federally funded research for grantee and contractor institutions is a separate reason to encourage Bayh-Dole patent rights for grantees and contractors as a matter of public policy, in addition to the rationale of creating incentives for private firms to license federally funded inventions from nonprofits and small businesses in order to invest in commercialization. The strongest arguments in favor of an explicit revenue-generation policy are that such revenue (1) rewards institutions that successfully discover commercially valuable inventions, thereby creating incentives for other institutions to emulate this socially laudable success; (2) channels revenues into research and education, both of which are largely public goods; and (3) would otherwise mainly be retained by the for-profit users of the technology.

If securing a share of revenues from valuable uses of university technology is accepted as a policy rationale, this case illustrates a need for oversight. Columbia's attempt to extend the patent term and enforcement of the 2002 patent after the original three patents expired in 2000 suggests that patent revenue was a potent incentive. The policy questions posed by this case include, How much is enough? And how long is long enough? What is the right balance of incentives for grantee and contractor institutions, such as universities, in reaping revenues from federally funded research inventions? What does government need to do to ensure that the revenue incentive does not expand without boundaries? Michael Crow's argument that university revenues are put to public purposes for research and education is valid, but it also is open-ended.

These questions usually are buried with other considerations of incentives for commercialization and with the wish to avoid inventions languishing in government and nonprofit laboratories for want of commercial incentives, which was the main justification for the Bayh-Dole

Act that was invoked between 1978 and 1980 during its legislative history (Berman 2008; Eisenberg 1996). Technologies exemplified by recombinant DNA (the Cohen-Boyer patents) and cotransformation technology (Axel patents) raise an alternative “fair rewards” rationale for university patenting. In these cases, there is little risk that technologies will languish without the patent incentive. Indeed, such inventions are not rare in academic research, for Cohen-Boyer and Axel patents are not the only highly lucrative platform technologies licensed by universities. Others are the fluorescent tagging of cells and large molecules used in fluorescent-activated cell sorting (Stanford), several City of Hope patents related to production of proteins from recombinant DNA, methods for making monoclonal antibodies (Stanford and Columbia), and small interfering RNA methods and constructs (Carnegie Institute and others). These technologies were rapidly adopted in both academic and for-profit biotechnology R&D and were fairly clear-cut cases in which a patent incentive was not needed to invest in further development of the technology itself to bring it to fruition, although in many cases, specific applications do require substantial investment (as did the products developed from the Axel patents). Cohen-Boyer and Axel patents also are clear cases in which universities gained financially from their technological success and captured a fraction of the resulting social benefit they would otherwise have forgone. This “fair rewards” rationale for the Bayh-Dole Act patent ownership rights warrants explicit attention as a consequence of the default ownership rules.

The Bayh-Dole Act does not list, as an explicit goal, channeling money to universities and small businesses to support research and education. Perhaps it should—or should not. The Axel patents suggest that policy should be discussed on its own merits, because the prospect of substantial revenues appears to drive some decisions about disposition of patents arising from federal grants and contracts. The Axel patents are a case in point and a good case to focus such a debate because it is quite clear that the science—both the science leading to the invention and the work of the principals afterward—was of very high quality. (Richard Axel went on to win the Nobel Prize [Axel 2004], and Wigler and Silverstein have had distinguished careers in science.) At the same time, real public accountability would require substantially more information about what Columbia did with the revenues. In theory, this should be possible to ascertain with the Axel patents, because the terms of the letter agreement with the government required annual reporting. Our FOIA

request to the U.S. Department of Health and Human Services, referred to the NIH, failed to produce such reports. NIH did not confirm or deny that they existed, but it was clear nothing had been done to monitor the terms of the Miller letter. Public accountability was limited at best. The Bayh-Dole Act stipulates that revenues be spent on research and education, similar to the letter agreement governing the Axel patents, but it is not clear that the government is any more capable of monitoring expenditures of technology-licensing revenues under Bayh-Dole than it appears to have been with the Axel patents. Public accountability for expenditures of technology licensing revenues is a matter that the General Accountability Office (GAO) might constructively address in one of its periodic assessments of Bayh-Dole activities.

As other countries adopt laws emulating the Bayh-Dole rules, revenue for universities may be a goal (So et al. 2008). This may prove to be a compelling argument. For example, developing nations' universities whose researchers discover patentable inventions may wish to license those inventions to corporations based in the developed world. The alternative is for discoveries arising in a developing country university to be exploited in the developed world, with little financial return to the originating research institution or its home country. As developing countries increasingly focus on building their R&D capacity, Bayh-Dole rules are apt to be attractive as ways to attract foreign corporations to fund developing-country universities. Although expectations are likely to exceed actual revenues (So et al. 2008), at least for many decades until the research institutions have attained substantial capacity to turn out lucrative technologies or in particularly fortunate research institutions, in the long run this argument has merit.

The Axel patents also raise questions for academic institutions about how aggressively to go after patent-licensing revenues. Columbia University's pursuit of patent extension after the original Axel patents expired in 2000 was very costly. First, the litigation expenses were undoubtedly substantial, as Columbia spent a significant amount of time and money on legal fees after being sued by eight licensees. In addition, although it is difficult to estimate the cost of pursuing a patent application for almost twenty-two years, it would certainly be considerable. Those costs may pale compared with the revenue stream, but the ratio of legal expenditure to revenue return probably turned negative after the original patents expired. What was the balance of *further* revenue compared with the cost of litigation for the 2002 patent, which

currently does not generate revenues and will not do so unless Columbia's long fight ends in the reissue of a patent (in which case the potential licensees have vowed to sue)? The initial Axel patents were clearly lucrative, but the efforts to extend the patent term after the initial patents expired may well have cost more than any revenues brought in. Indeed, legal and procedural costs for Columbia continue to this day, three decades after the story began. Only Columbia knows how much they are, but the case for its actions after the initial patents expired in 2000 is weak, certainly on policy grounds and probably on financial grounds as well.

Why would an institution like Columbia fight so hard for a patent extension and new patents beyond the term of the original patents? One obvious answer is patent royalties. Columbia's reliance on royalty-based revenue may have made it work hard to keep the revenue stream flowing. This illustrates two problematic aspects of the "fair reward" rationale for Bayh-Dole patent rights: First, if universities depend on royalties from patent licenses, they may also take extreme measures to maintain them. Second, it suggests a need for stronger government oversight of the benefits it confers through Bayh-Dole patent rights and checks on abuses of the strong incentives to generate revenues arising in federally funded research when patents achieve blockbuster status. Another problem with this "winner's curse" is its skewness, because only a lucky few institutions will reap the rewards. Most patent royalties come from "blockbuster" patents like the Cohen-Boyer and Axel patents, which are few and far between (Thursby and Thursby 2007). The harder that universities push industry to pay patent royalties, the more likely it is that they will incur ill will, provoke litigation, and invite Congress to revise the Bayh-Dole Act.

Interview Methods

Alessandra Colaianni conducted three interviews in the summer and fall of 2005 during the preparation of this article, with Robert Cook-Deegan joining her in the Wigler interview. Interviews with Saul Silverstein, Michael Wigler, and Paul A. Marks were on the record and were recorded using a standard tape recorder. All the interviewees gave oral informed consent, in accordance with Duke University's IRB (Duke University IRB Protocol 1277). Those interviews not "on the record"

are protected by a certificate of confidentiality issued by the National Human Genome Research Institute (also in association with Duke IRB Protocol 1277). All three interviewees were given the opportunity to respond to their statements and points attributed to them. Two interviewees made minor suggestions that we adopted, and one interviewee did not respond. Silverstein and Wigler were chosen as interviewees because they are listed as inventors on the cotransformation patents; Richard Axel, also an inventor, did not respond to our repeated requests for interviews or comment. Paul A. Marks was chosen because during our interview with Silverstein, it became apparent that Marks had played a significant administrative role.

Endnotes

1. See 35 USC 200.
2. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
3. 35 U.S.C. 121 "Divisional Applications." Appendix L. Patent Laws. Available at http://www.uspto.gov/web/offices/pac/mpep/documents/appxl_35_U_S_C_121.htm (accessed September 25, 2007).
4. 35 U.S.C. 120 "Benefit of Earlier Filing Date in the United States." Appendix L. Patent Laws. Available at http://www.uspto.gov/web/offices/pac/mpep/documents/appxl_35_U_S_C_120.htm (accessed September 25, 2007).
5. *Biogen Idec MA Inc., et al., Plaintiffs, v. The Trustees of Columbia University in the City of New York, Defendant*. 332 F. Supp. 2d 286; 2004. U.S. Dist. LEXIS 16315.
6. Columbia University was also granted thirteen international or world patents: WO810-2426A1 (World); JP57500410T2; JP07095880A2; JP06030588B4; JP02736502B2 (Japan); HK0059992A (Hong Kong); EP0045809B1; EP0045809A1 (European Patent Office); DE3176369C0 (Germany); CA1179953A1 (Canada); AU7037881A1; AU0558061B2 (Australia); and AT0029042E (Austria).
7. *Trustees of Columbia University in the City of New York, Plaintiff, v. Roche Diagnostics GmbH, formerly known as Boehringer Mannheim GmbH, Defendant*. 150 F. Supp. 2d 191; 2001 U.S. Dist LEXIS 6383.
8. Personal communication, Michael Cleare, former executive director of Columbia's Science and Technology Ventures Office, to Richard R. Nelson, Henry R. Luce professor of international political economy at Columbia University, and Bhaven Sampat, assistant professor of health policy and management, Mailman School of Public Health, Columbia University; August 29, 2006. Forwarded with permission to the authors.
9. Details about the fourth person and the share he or she received were not shared.
10. The revenues earned from technology licensing are not entirely attributable to patents (some technologies are licensed without a patent), nor are technology licensing revenues entirely devoted to research. Licensing revenues are often used to support the technology licensing operations, for example, or fellowships, education, and indirect costs of research. Technology licensing revenues are, however, an upper limit on what fraction of the institution's research *could* be funded from technology licensing, compared with other R&D funding sources. The ratio of technology licensing revenues to R&D expenditures is therefore only an indicator of how much an institution relies on technology licensing to fund research, but it is a defensible proxy measure of "royalty dependency" in a university's R&D funding stream.

11. This does not imply that technology licensing revenues accounted for this fraction of R&D. Rather, as noted in the previous note, it indicates the maximum fraction of R&D that *could* be covered by technology-licensing income, depending on how that particular institution allocates the funds generated by such licensing.
12. See Bureau of National Affairs, *Columbia Covransformation Patent Extension*, 5. HEALTH CARE DAILY (BNA) 7 (May 17, 2000). Available at <http://www.cptech.org/ip/health/biotech/bna.html> (accessed December 1, 2008). The mechanism might have faced challenge even if passed, since the Hatch-Waxman provisions do not apply to biologics and drugs equally. That is, most or all products covered by the Axel patents are approved by the FDA as biologics, not drugs.
13. See Sen. Res. 2536, 106th Cong., Sec. 2801.
14. A complete comparison of the '275 patent's claims to the earlier Axel patents' claims is beyond the scope of this paper. Interested readers are encouraged to see Dudzinski 2004 and Ravicher 2004 for side-by-side legal analyses of the differences between the '275 patent and the prior Axel patents.
15. *Biogen Idec MA Inc., et al., Plaintiffs, v. The Trustees of Columbia University in the City of New York, Defendant*. 332 F. Supp. 2d 286; 2004 U.S. Dist. LEXIS 16315.
16. Ravicher argued that the claims from the prior Axel patents were different from the claims in the '275 patent in name only; that though the wording of the claims was slightly different, the essential technology claimed was the same. Interested readers are encouraged to see Ravicher 2004 for the full analysis.
17. United States Patent and Trademark Office, Patent Application Information Retrieval, Application 90/006,953, "DNA Construct for Producing Proteinaceous Materials in Eucaryotic Cells." Available at http://portal.uspto.gov/external/portal/?ut/p/kcxml/04_Sj9SPyKssy0xPLMnMz0vM0Y_QjzKLN4gPMATJgFieAfqRqCLGpugijnABX4_83FT9IKB_EpDIQxNDCRz8qJzU9MbIsp1jfWz9AvyA3NDSi3NsRAHxEBJg!/delta/base64xml/L0lJSk03dWIDU1IKSi9vQXNd3QUFNWWdBQ0VJUWhDRUVJaEZLQSEvNEZH2RZbktKMEZSb1hmckNIZGgvN18wXzE4TC8yMC9zYS5nZXRCaWI!#7_0_18L (accessed July 22, 2008).
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19. *Biogen Idec MA Inc., et al., Plaintiffs, v. The Trustees of Columbia University in the City of New York, Defendant*. 332 F. Supp. 2d 286; 2004 U.S. Dist. LEXIS 16315.

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